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Aneuploidy Among Prenatally Detected Neural Tube Defects

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We have reported previously a 10% aneuploidy detection rate among 39 cases of fetal neural tube defects (NTD). Subsequently we amassed an additional experience of over 17,000 prenatal diagnosis cases over a 5-year period. During this period 106 cases of NTDs were identified; 44 with anencephaly, 62 with open spina bifida. The average maternal age of this population with NTDs was 29 years (15–40); 6 patients declined amniocentesis. Six of 100 cytogenetic studies were aneuploid; one anencephalic fetus had inherited a maternal marker chromosome, and 5 NTD cases had trisomy 18. The average maternal age of the aneuploid cases was 31 (19–40); 3 were 35 years or older. Four of 5 trisomy 18 cases had multiple congenital anomalies (MCA). The overall aneuploidy detection rate in our cohort was 5–6%, while aneuploidy occurred in 2% of the isolated NTD cases, and 24% of the MCA cases. Combining the earlier experience, 4/39 aneuploidy (2 trisomy 18, 4p+, del 13q) yields an aneuploidy detection frequency of 10/145 (7%), of which most (7/10) had trisomy 18. These data support fetal karyotyping for accurate diagnosis, prognosis, and recurrence-risk counseling. © 1996 Wiley-Liss, Inc.

KEY WORDS: prenatal diagnosis, neural tube defects, aneuploidy, trisomy 18

INTRODUCTION

Prenatal diagnosis of neural tube defects has been greatly facilitated by maternal serum screening programs and improved sonographic techniques. However, the presence of associated anomalies and aneuploidy remain critical factors in determining underlying cause, prognosis, management, and recurrence risks. We have previously reported a detection rate of 10% aneuploidy among 39 cases of fetal neural tube defects (NTD) [Drugan et al., 1989]. Subsequently, we amassed an experience of over 17,000 prenatal diagnosis cases over a 5-year period. This experience has been evaluated further to explore the association of aneuploidy in the fetus with a neural tube defect, and identify any antecedents of increased risk.

MATERIALS AND METHODS

A cohort study was based on the prenatal cases from the Center for Fetal Diagnosis and Therapy between April 1989 and October 1994. Ultrasound records were classified according to the detection of fetal anomalies; anencephaly, spina bifida, and associated anomalies (MCA). Genetics charts were reviewed for maternal age, mode of ascertainment, maternal serum analytes results, and fetal karyotype. We performed categorical and multivariate analyses of anomalies, stratified for maternal age.

RESULTS

Of the 17,053 patients studied, 1,003 cases had sonographic anomaly(ies), a 5.8% detection rate. The 106 cases of NTD among these 1,003 sonographically abnormal cases are the focus of this study; 44 had anencephaly, and 62 had open spina bifida (NTD). Neural tube defects accounted for over 10% of the sonographic aberrant cases during this study period. The average maternal age of the study population was 29 years (15–40); 6 of the patients declined amniocentesis. Aneuploidy was detected in 6 of 100 cytogenetic studies; one case of anencephaly had an inherited maternal marker chromosome, and 5 cases with open spina bifida had trisomy 18. The average maternal age of the aneuploid cases was 31 (19–40); 3 were 35 years or older. Four of 5 trisomy 18 cases had multiple congenital anomalies (MCA). A summary of findings is presented in Table I.

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TABLE I. Summary of Findings Categorized by Types of Neural Tube Defect, Maternal Age, Aneuploidy, and Aneuploidy Rate

		AMA[a] (>34)		MSAFP[d] abnl			
Anomaly	Mean age (yr)	n	(%)	n	(%)	Aneuploidy	Rate (%)
Anencephaly	27 (15–40)	5/44	(11)	21/44	(48)	1/44, +marker	2
Isolated NTD[b]	28 (15–40)	5/45	(11)	19/45	(42)	1/45, 47+18	2
NTD + MCA[c]	30 (19–40)	3/17	(18)	6/17	(35)	4/17, 47+18	24
Total n = 106	mean age = 29	13/106	(12)	46/106	(43)	6/106 (5.7%)	5–6

[a]AMA, advanced maternal age for age greater than or equal to 35.
[b]NTD, lumbosacral neural tube defects.
[c]MCA, multiple congenital anomalies of other organ systems.
[d]MSAFP, abnormal maternal serum alpha fetoprotein.

The clinical findings of the abnormal karyotype cases are presented in Table II. Three of 13 (23%) AMA cases with NTD were found to have aneuploidy, compared with 3 of 87 in the younger age group, a 3.4% aneuploidy detection rate. The expected significant difference in the maternal age among the aneuploid versus euploid cases is present ($\chi^2 = 4.6$, df = 1, $P < 0.05$). The expected age-adjusted risk for trisomy 18 is reported to be 0.1–1.2/1,000, which is significantly lower than the observed frequency in this cohort with prenatally detected NTD.

Combining our earlier experience of 4/39 aneuploidy (2 trisomy 18, 4p+, del 13q), which is not included in this 5-year data set, results in a total of 10 aneuploidies detected among 145 sonographically detected NTD for an overall aneuploidy rate of 7%. In our experience trisomy 18 was present in 7/145 (5%) of the NTD cases.

DISCUSSION

Our findings clarify the increased risk of aneuploidy in the fetus with a prenatally detected neural tube defect, especially when they are MCA. This increased risk is not completely explained by maternal age, previous history, or a priori risk assessment. The association of advanced maternal age, and/or multiple congenital anomalies in other organ systems, predicts a high aneuploidy detection rate, >23%. However, this increased risk for aneuploidy is not limited to advanced maternal age or MCA. Isolated spina bifida has the least increased risk for aneuploidy of approximately 2%, even among the younger age group. Neural tube defects associated with multiple congenital anomalies have the highest increased risk for aneuploidy, approximately 24%, findings consistent with previous reports [Dombrowski et al., 1993].

The peculiar association of trisomy 18 and prenatally detected neural tube defects is consistent with reports based on pediatric cases of trisomy 18 [Hecht and Hecht, 1990]. However, the observed frequency of this prenatal association is much higher than previously reported. One of our cases had a small isolated sacral NTD; this was a 22-year-old patient with no antecedent risk factors. Trisomy 18 was discovered on karyotypic analysis in the midst of prenatal evaluation for expected neonatal surgical repair of this good-prognosis anatomic defect. Of importance in prenatal counseling are the most recent reports on increased survival in trisomy 18 [Root and Carey, 1994]. Life expectancy is longer than previously held, and is associated with significant morbidity.

The critical need for accurate diagnoses in congenital anomalies goes beyond the physical findings and must include the potential underlying causal explanation of "why this anomaly in this fetus?" Aneuploidy confers not only a likely genetic cause, but also drastically different prognosis as well as recurrence risk estimates. Furthermore, when aneuploidy is present the prenatal diagnostic steps in subsequent pregnancies can then be directed towards early ascertainment of fetal karyotype. If the association of NTD with multiple anomalies is syndromic, the focus of genetic counseling is altered to reflect that syndrome's cause. If no syndrome or aneuploidy is found, the most likely explanation is multifactorial determination. It is in this subset of patients (fortunately most), that preconceptional folate supplementation may actually reduce the recurrence risk from approximately 4% to 1% [Crandall et al., 1995].

TABLE II. Summary of Abnormal Karyotype Cases; NTD Type; Isolated or Multiple Anomalies, and Maternal Age

Anomaly type (Anencephaly)	Karyotype (Marker)	History and maternal age (37 years, Celtic, + family history)
Isolated spinal NTD	Trisomy 18	22 years, unremarkable family history
Sacral NTD and MCA	Trisomy 18	19 years, late pregnancy care
LS NTD[a] and MCA[b]	Trisomy 18	32 years, unremarkable family history
LS NTD and MCA	Trisomy 18	35 years, unremarkable family history
LS NTD and MCA	Trisomy 18	40 years, unremarkable family history

[a] LS NTD, lumbosacral neural tube defects.
[b] MCA, multiple congenital anomalies of other organ systems.

The specific recurrence risk will vary with each case depending on findings at autopsy, karyotype, and pedigree analysis. However, the findings of this report support the critical role of fetal karyotypic analysis for accurate diagnosis, prognosis and recurrence-risk counseling when a NTD is identified during sonographic prenatal screening.

Therefore, our data also stress the importance of a thorough ultrasound exam to search for associated anomalies when a NTD is found since the likelihood of aneuploidy varies markedly. In an era when cost-consciousness is paramount, some may argue that in the absence of MCA, karyotyping would not be indicated. However, in our opinion, the 20% yield in our data with isolated NTD's is still high enough to warrant karyotyping. Further data may better clarify these points.

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